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## Hypersensitivity of vascular alpha-adrenoceptor responsiveness: A possible inducer of pain in neuropathic states

Robert W. Teasell  
*Lawson Health Research Institute*

Qingping Feng  
*Schulich School of Medicine & Dentistry*

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● LETTERS TO THE EDITOR

## Hypersensitivity of vascular alpha-adrenoceptor responsiveness: a possible inducer of pain in neuropathic states

Dear editor,

Dr. Peter Drummond's article noted that peripheral nerve and tissue injury in neuropathic pain syndromes releases cytokines which in turn lead to an increase in alpha1-adrenoceptor upregulation, resulting in a heightened sensitivity to noradrenaline. In these circumstances, noradrenaline acting on upregulated alpha1 a-adrenoceptors increases the release of cytokine interleukin-6. Hence, nociceptive afferent neurons exposed to injury induced cytokines become more hypersensitive to noradrenaline, which in turn promotes the release of more inflammatory cytokines. Dr. Drummond noted that this mechanism may contribute to the pain of post-herpetic neuralgia or complex regional pain syndrome (Drummond, 2014).

Using a technique that allowed us to monitor vasoconstriction in peripheral veins of affected limbs in response to increasing concentrations of noradrenaline in local intravenous infusions, we were able to determine the responsiveness of alpha-adrenoceptors in a number of painful conditions. We found significant venous alpha-adrenoceptor hyperresponsiveness in complex regional pain syndrome (Arnold et al., 1993), spinal cord injuries (Arnold et al., 1995; Teasell et al., 2000) and diabetic peripheral nerve injuries (Capes et al., 1997) to local intravenous infusions of noradrenaline.

A similar technique in insulin dependent diabetic mellitus patients found vascular (venous) responsiveness to noradrenaline directly correlated with nerve conduction velocity, a measure of the severity of the nerve injury (Eichler et al., 1992; Bodmer et al., 1999). Notably, the ED50 (defined as the concentration of noradrenaline required to cause a 50% reduction of the resting vein diameter) of the dorsal veins of insulin dependent diabetic mellitus patients with symptomatic autonomic dysfunction was lower than in asymptomatic diabetics. The exaggerated vascular reactivity to noradrenaline can be blocked by an alpha 1-adrenoceptor blocker doxazosin, suggesting the vascular response is mediated by alpha-1 adrenoceptors.

One hypothesis which may account for these findings is a dysfunctional sympathetic nervous system with diminished ability of alpha-2 adrenoceptors to presympathetically reuptake noradrenaline resulting in excessive stimulation of the alpha-1 adrenoceptor. Support for this comes from observations of higher noradrenaline levels in patients with a clinical diabetic peripheral neuropathy (Capes et al., 1997) and the fact that transdermal clonidine (an alpha-2-adrenoceptor agonist) is more effective than controls in reducing the pain of peripheral diabetic neuropathies (Zeigler et al., 1992).

This additional evidence, which demonstrates alpha-adrenoceptor hyperresponsiveness of peripheral veins in three painful neuropathic states, insulin dependent diabetic mellitus, spinal cord injuries and diabetic peripheral neuropathies, raises the intriguing possibility that sympathetic nervous system dysfunction may be an important factor in the generation of pain in a num-

ber of neuropathic states (Teasell and Arnold, 2004). This is also supported by the fact that alpha-adrenoceptor blockers relieve pain in diabetic neuropathy in rodents (Lee et al., 2000; Bujalska et al., 2008) and in patients with chronic prostatitis/chronic pelvic pain syndrome (Thakkinstian et al., 2012).

Robert W. Teasell\*, Qingping Feng  
Aging, Rehabilitation, and Geriatric Care, Lawson Health Research Institute, St. Joseph's Parkwood Institute, London, Ontario, Canada (Teasell RW)  
Department of Physical Medicine and Rehabilitation, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada (Teasell RW)  
Departments of Physiology & Pharmacology, and Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada (Feng Q)

\*Correspondence to: Robert W. Teasell,  
Robert. Teasell@sjhc.london.on.ca.

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